Greater Blood Pressure Variability Is Associated With Lower Cognitive Performance

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The Maastricht Study

Tan Lai Zhou, Abraham A. Kroon, Thomas T. van Sloten, Martin P.J. van Boxtel, Frans R.J. Verhey, Miranda T. Schram, Sebastian Köhler, Coen D.A. Stehouwer, Ronald M.A. Henry

Abstract—An increasing number of individuals will face age-related cognitive difficulties because life expectancy has increased. It is, therefore, important to identify modifiable risk factors for cognitive impairment. Very short–term to mid-term blood pressure variability (BPV) may be such a factor because it may cause cerebral ischemia. To this end, we investigated whether greater systolic and diastolic BPV are cross-sectionally associated with memory function (n=1804), information processing speed (n=1793), and executive function (n=1780) in 40- to 75-year-old individuals from The Maastricht Study. A composite BPV-index was derived by standardizing within-visit, 24-hour, and 7-day BPV. We performed linear regression with adjustments for age, sex, educational level, 24-hour systolic or diastolic pressure, and cardiovascular risk factors. We found that a 1-SD greater systolic BPV was not associated with information processing speed (β [SD difference], −0.10; 95% CI, −0.14 to 0.06), or executive function (−0.09; 95% CI, −0.20 to 0.02) but was marginally associated with lower memory function (−0.11; 95% CI, −0.21 to 0.00). A 1-SD greater diastolic BPV was associated with lower information processing speed (−0.10; 95% CI, −0.20 to −0.00) and executive function (−0.12; 95% CI, −0.22 to −0.01) and marginally associated with lower memory function (−0.09; 95% CI, −0.20 to 0.01). These effects on cognitive performance are equivalent to ≈3 additional years of aging. In conclusion, greater very short-term to mid-term diastolic and, to a lesser extent, systolic BPV may be a modifiable risk factor for cognitive deterioration in 40- to 75-year-old, community-dwelling individuals. **(*Hypertension*. 2019;73:803-811. DOI: 10.1161/HYPERTENSIONAHA.118.12305.)** ● **Online Data Supplement**

Key Words: aging ■ blood pressure ■ executive function ■ memory ■ risk factor

Life expectancy has increased globally over the past decades, which implies that an increasing number of individuals will face cognitive difficulties or even dementia because of aging.[1,2] It is, therefore, important to identify potential modifiable causes of cognitive impairment to prevent cognitive decline. We hypothesize that greater very short- to mid-term blood pressure variability (BPV) may be a modifiable[3] risk factor.

Greater BPV may contribute to lower cognitive performance by 2 mechanisms. First, the brain microvasculature has a relatively low microvascular impedance. Greater pulsatile pressure loads (ie, greater BPV) may, therefore, penetrate deeply into the vasculature, and hence lead to microvascular damage.[4,5] Second, decreased perfusion may occur with (excessive) falls in blood pressure (BP), especially when cerebral autoregulation is impaired.[6] Cerebral microvascular damage and falls in BP may, in turn, lead to ischemia, structural brain abnormalities, and ultimately lower cognitive performance.

Indeed, previous studies have suggested that greater BPV and lower cognitive performance are associated.[7–16] However, these studies have focused mainly on long-term (ie, visit-to-visit) BPV,[7–12] have targeted old to very old individuals,[11–14] have evaluated cognitive performance by only a single, global test (eg, Mini-Mental State Examination),[15–17] or did not adjust for important confounders, such as mean BP and use of antihypertensive medication.[18,19]

To address the issues stated above, we investigated the association between BPV along the very short- to mid-term range (ie, within-visit, 24-hour, and 7-day) BPV and 3 domains of cognitive performance (ie, memory function [MF], information processing speed [IPS], and executive function [EF]) in 40- to 75-year-old participants from the population-based Maastricht Study.

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From the Department of Internal Medicine (T.L.Z., A.A.K., M.T.S., C.D.A.S., R.M.A.H.), Department of Psychiatry and Neuropsychology, Alzheimer Centre Limburg (M.P.J.v.B., F.R.J.V., S.K.), and Heart and Vascular Centre (M.T.S., R.M.A.H.), Maastricht University Medical Centre, the Netherlands; CARIM School for Cardiovascular Diseases (T.L.Z., A.A.K., T.T.v.S., M.T.S., C.D.A.S., R.M.A.H.) and MHeNs School for Mental Health and Neuroscience (M.P.J.v.B., F.R.J.V., S.K.), Maastricht University, the Netherlands; Faculté de Médecine, Université Paris Descartes, Sorbonne Paris Cité, France (T.T.v.S.); and Department of Epidemiology and Department of Arterial Mechanics, INSERM, UMR-S970, Paris Cardiovascular Research Center, France (T.T.v.S.).

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Correspondence to Ronald M.A. Henry, Department of Internal Medicine, Maastricht University Medical Centre, P. Debyelaan 25, PO Box 5800, 6202 AZ, Maastricht, the Netherlands. Email rma.henry@mumc.nl

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Methods

The Maastricht Study

We used data from The Maastricht Study, an observational prospective population-based cohort study. The rationale and methodology have been described previously.[20] In brief, the study focuses on the etiology, pathophysiology, complications, and comorbidities of type 2 diabetes mellitus (T2DM) and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 years and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns and from the municipal registries and participants with T2DM through the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2DM status, with an oversampling of individuals with T2DM, for reasons of statistical efficiency. The present report includes cross-sectional data from the first 3451 participants. The examinations of each participant were performed within a time window of 3 months. The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare, and Sports of the Netherlands (Permit 131088-105234-PG). All participants gave written informed consent. Data are available from The Maastricht Study for any researcher who meets the criteria for access to confidential data, and the corresponding author may be contacted to request data.

Data collection

BP Measurements and BPV

A detailed description of the office, 24-hour ambulatory, and 7-day home BP measurements and variability have been reported previously.[21] Briefly, within-visit BPV was calculated as the SD of 3 consecutive office BP measurements, with a 1-minute interval, after 10 minutes of rest. Twenty-four hour BPV was calculated as the average real variability of BP readings taken every 15 minutes between 08:00 AM to 23:00 PM, and every 30 minutes between 23:00 PM to 08.00 AM, 7-day BPV was calculated as the SD of home BP measurements taken twice, with a 1-minute interval, each morning, and evening, for 7 consecutive days. We calculated a composite index of BPV of within-visit, 24-hour, and 7-day BPV, for reasons of statistical efficiency: first, it reduces the biological variability of each individual measure,[22] as we hypothesize that the (patho)physiological mechanisms underlying the association between greater BPV and worse cognitive performance overlap. Second, it reduces the chance of a type I error. This approach is justified when the individual measures within a composite index all associate in the same direction with the outcome.[23] The individual measures were standardized into *Z* scores (individual value/population mean/population SD). The individual measures were then summed and averaged into the composite index of systolic and diastolic BPV.

Cognitive Performance

Cognitive performance was assessed by a concise (30-minute) neuropsychological test battery.[20] For conceptual clarity, test scores were standardized and divided into 3 cognitive domains (ie, MF, IPS, and EF). A detailed description of neuropsychological tests and methods used to calculate domain scores is provided in the Methods in the online-only Data Supplement. Briefly, MF was evaluated using the Verbal Learning Test[24] by calculating the standardized average of total immediate and delayed recall scores. The composite score for IPS was derived from the Stroop Color-Word Test Part I and II,[25] the Concept Shifting Test Part A and B,[26] and the Letter-Digit Substitution Test.[27] EF was assessed by the Stroop Color-Word Test Part III and the Concept Shifting Test Part C. If necessary, individual test scores were log-transformed to fulfill the normality assumption or inverted so that higher scores indicated better cognitive performance. After selection of the final study population, cognitive performance test scores were standardized again to maintain a mean of zero and SD of 1.

Covariates

Alcohol consumption, smoking status, educational level, history of cardiovascular disease (CVD), and moderate-to-vigorous physical activity were assessed by questionnaire. Alcohol consumption was defined as nonconsumer, low-consumer (≤7 alcoholic drinks/wk for women; ≤14 alcoholic drinks/wk for men), and high-consumer (>7 alcoholic drinks/wk for women; >14 alcohol drinks/wk for men). Smoking status was categorized into never, former, and current smoker. Educational level was classified into 3 groups: low (none, primary or lower vocational education only), intermediate (intermediate general secondary, intermediate vocational or higher general secondary education), and high (higher vocational education or university level of education). Body mass index (BMI), waist circumference, total cholesterol, HDL (high-density lipoprotein) cholesterol,

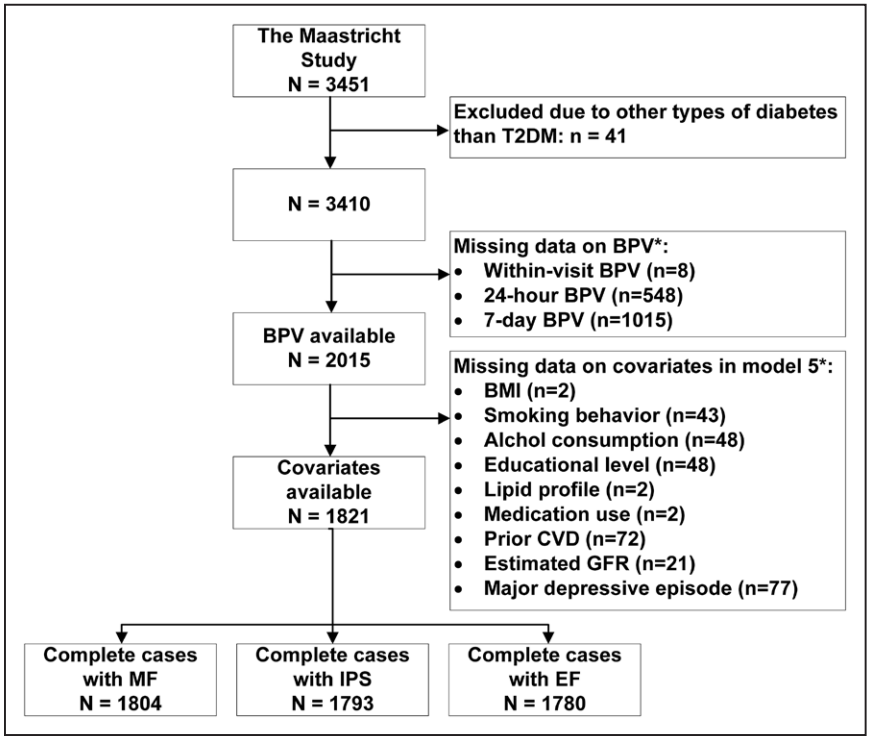

Figure 1. Flow diagram delineating the selection of the final study populations. BMI, body mass index; BPV, blood pressure variability; CVD, cardiovascular disease; EF, executive functioning; GFR, glomerular filtration rate; MF, memory function; IPS, information processing speed; and T2DM, type 2 diabetes mellitus. *Not mutually exclusive.

Table 1. Clinical Characteristics of the Study Population (With Complete Memory Function) According to Tertiles of Systolic Blood Pressure Variability

Characteristic	Memory Function	Tertiles of Composite Systolic Blood Pressure Variability		
	Population, n=1804	Tertile 1 (Low), n=601	Tertile 2 (Middle), n=602	Tertile 3 (High), n=601
Demographics				
Age, y	59.8±8.0	57.7±8.6	60.1±7.6	61.5±7.6
Men	936 (51.9%)	323 (53.7%)	311 (51.7%)	302 (50.2%)
Educational level				
Low	287 (15.9%)	84 (14.0%)	105 (17.4%)	98 (16.3%)
Intermediate	786 (43.6%)	260 (43.3%)	249 (41.4%)	277 (46.1%)
High	731 (40.5%)	257 (42.8%)	248 (41.2%)	226 (37.6%)
Cardiovascular risk factors				
BMI, kg/m^2	27.0±4.3	26.3±4.2	26.9±4.1	27.7±4.4
Glucose metabolism status				
Normal glucose metabolism	1025 (56.8%)	395 (65.7%)	354 (58.8%)	276 (45.9%)
Prediabetes	269 (14.9%)	84 (14.0%)	89 (14.8%)	96 (16.0%)
Type 2 diabetes mellitus	510 (28.3%)	122 (20.3%)	159 (26.4%)	229 (38.1%)
Triglycerides, mmol/l	1.2 [0.88–1.71]	1.1 [0.8–1.5]	1.2 [0.9–1.7]	1.3 [1.0–1.9]
Total-to-HDL cholesterol ratio	3.7±1.2	3.7±1.2	3.7±1.1	3.8±1.2
History of cardiovascular disease	303 (16.8%)	85 (14.1%)	109 (18.1%)	109 (18.1%)
eGFR, ml/(min·1.73m^2)	88.4±14.6	90.6±14.4	87.8±14.1	86.6±15.1
Lifestyle variables				
Smoking behavior				
Never	646 (35.8%)	247 (41.1%)	186 (30.9%)	213 (35.4%)
Former	937 (51.9%)	286 (47.6%)	336 (55.8%)	315 (52.4%)
Current	221 (12.3%)	68 (11.3%)	80 (13.3%)	73 (12.1%)
Alcohol consumption				
None	342 (19.0%)	93 (15.5%)	116 (19.3%)	133 (22.1%)
Low	993 (55.0%)	377 (62.7%)	329 (54.7%)	287 (47.8%)
High	469 (26.0%)	131 (21.8%)	157 (26.1%)	181 (30.1%)
Medication				
Use of antihypertensive medication	706 (39.1%)	183 (30.4%)	229 (38.0%)	294 (48.9%)
β-Blockers	309 (17.1%)	91 (13.5%)	99 (15.8%)	133 (22.1%)
Calcium channel blockers	163 (9.0%)	49 (8.2%)	57 (9.5%)	57 (9.5%)
ACE inhibitors	224 (12.4%)	40 (6.7%)	69 (11.5%)	115 (19.1%)
Angiotensin II receptor blockers	315 (17.5%)	86 (14.3%)	112 (18.6%)	117 (19.5%)
Diuretics	285 (15.8%)	68 (11.3%)	98 (16.3%)	119 (19.8%)
Lipid-modifying medication	651 (36.1%)	186 (30.9%)	205 (34.1%)	260 (43.3%)
24-hour SBP, mm Hg	120.0±11.6	116.1±9.3	119.6±11.1	124.4±12.8
24-hour DBP, mm Hg	74.3±7.1	72.8±6.3	74.2±6.9	76.0±7.7
BPV parameters				
Within-visit systolic BPV, mm Hg	4.6±2.8	2.8±1.5	4.4±2.0	6.6±3.1
Within-visit diastolic BPV, mm Hg	2.5±1.7	2.1±1.3	2.4±1.5	2.9±2.1
24-hour systolic BPV, mm Hg	10.0±2.5	8.2±1.4	9.9±1.5	12.0±2.7
24-hour diastolic BPV, mm Hg	6.9±1.8	6.2±1.4	6.8±1.6	7.8 ±2.1
7-day systolic BPV, mm Hg	9.2±3.8	6.9±1.7	8.7±2.2	12.0±4.7

(*Continued*)

Table 1. Continued

Characteristic	Memory Function	Tertiles of Composite Systolic Blood Pressure Variability		
	Population, n=1804	Tertile 1 (Low), n=601	Tertile 2 (Middle), n=602	Tertile 3 (High), n=601
7-day diastolic BPV, mm Hg	5.7±2.9	4.8±1.7	5.4±1.8	7.1±4.1
Mental health and cognitive performance				
Current major depressive episode	64 (3.6%)	22 (3.7%)	16 (2.7%)	26 (4.4%)
Memory function	0.00±1.00*	0.11±0.93	0.03±0.98	−0.13±1.03
Information processing speed†	0.00±1.00*	0.13±0.99	−0.01±0.97	−0.13±1.02
Executive function‡	0.00±1.00*	0.17±1.04	−0.03±0.96	−0.13±0.98

Data are presented as n (%), mean±SD, or median (interquartile range). ACE indicates angiotensin-converting enzyme; BMI, body mass index; BPV, blood pressure variability; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; and SBP, systolic blood pressure.

*Mean of zero and SD of 1 by definition, see Methods section.

†Value shown for individuals with complete information processing speed data.

‡Value shown for individuals with complete executive function data.

LDL (low-density lipoprotein) cholesterol, triglycerides, fasting glucose, postload glucose, and glycosylated hemoglobin were determined as described elsewhere.[20] Glucose metabolism status was categorized into normal glucose metabolism, prediabetes (impaired fasting glucose or impaired glucose tolerance), and T2DM, according to the World Health Organization 2006 criteria.[28] Estimated glomerular filtration rate was computed with the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula, using serum creatinine and cystatin C.[29] Information on the use of lipid-modifying and antihypertensive medication were collected during an interview. A current major depressive episode was assessed by the Mini-International Neuropsychiatric Interview.[30]

Statistical Analysis

All data were analyzed using IBM SPSS software version 23.0 for Windows (IBM Corp, Somers, NY). Data are presented as n (%), mean±SD, or median (interquartile range). We constructed tertiles of composite systolic and diastolic BPV. Associations between composite systolic and diastolic BPV and the composite scores of cognitive performance domains were examined with the use of multiple linear regression (lowest BPV tertile: reference category). Model 1 was adjusted for age, sex, and glucose metabolism status. Model 2 was additionally adjusted for 24-hour mean systolic or diastolic BP (where appropriate). Model 3 was additionally adjusted for lifestyle factors (ie, BMI, alcohol consumption, smoking status, and educational level). Model 4 was additionally adjusted for CVD risk factors (ie, estimated glomerular filtration rate, total-to-high density lipoprotein cholesterol ratio, triglycerides, lipid-modifying, and antihypertensive medication classes [β-blockers, calcium channel blockers, ACE (angiotensin-converting enzyme) inhibitors, angiotensin II receptor blockers, and diuretics separately]). Model 5 was additionally adjusted for prior CVD and current major depressive episode. Several additional analyses were performed. First, we included interaction terms in model 5 to examine whether any associations were modified by age, sex, or glucose metabolism status. Second, we additionally adjusted for moderate-to-vigorous physical activity and waist circumference or waist-to-hip ratio instead of BMI. Third, we evaluated the association between each individual BPV-index (ie, within-visit, 24-hour and 7-day BPV) and the cognitive performance domains separately. A 2-sided P value of <0.05 was considered statistically significant, except for the interaction analyses, where we used P<0.10.

Results

Study Population

Figure 1 shows the delineation of our study population. Participants with missing data had a higher BMI, lower total cholesterol levels, higher 7-day systolic BPV, and higher 24-hour and 7-day diastolic BPV, and lower MF scores, and IPS than those with complete data (Table S1 in the online-only Data Supplement).

Table 1 shows the characteristics of the study population with complete MF data according to tertiles of composite BPV (tertile 1: lowest BPV). In general, participants with the highest as compared to the lowest BPV were older, more often women, received lower education more often, had a worse CVD risk profile, and more often used antihypertensive medication. In addition, participants with the highest as compared to the lowest BPV had lower scores on cognitive performance.

Systolic BPV and Cognitive Performance

After adjustment for age, sex, glucose metabolism status (model 1), and 24-hour mean systolic BP (model 2), high systolic BPV was statistically significantly associated with a lower MF as compared to the lowest tertile of systolic BPV (regression coefficient [β, as SD difference] and 95% CI, −0.118; −0.226 to −0.010; Table 2; Figure 2). No statistically significant associations were observed with IPS (−0.045; 95% CI, −0.519 to 0.062) and EF (−0.082; 95% CI, −0.195 to 0.030). After further adjustment for estimated glomerular filtration rate, total-to-HDL cholesterol ratio, triglycerides, antihypertensive and lipid-modifying medication (model 4), prior CVD, and current depression (model 5), the associations attenuated and MF was lower in individuals with a high systolic BPV as compared to those with low systolic BPV, but did not reach statistical significance (−0.106; 95% CI, −0.213 to 0.001). In addition, systolic BPV was not statistically significantly associated with IPS (−0.039; 95% CI, −0.142 to 0.064) and EF (−0.087; 95% CI, −0.195 to 0.022).

Diastolic BPV and Cognitive Performance

After adjustment for the covariates of model 2, and with the lowest tertile of diastolic BPV as reference category, high diastolic BPV was statistically significantly associated with lower performance in all cognitive domains: MF (−0.123; 95% CI, −0.226 to −0.019), IPS (−0.137; 95% CI, −0.239 to

Table 2. Associations Between Systolic Blood Pressure Variability and Various Domains of Cognitive Performance

Model	Composite sBPV	Cognitive Performance Domains					
		Memory Function		Information Processing Speed		Executive Function	
		β (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value
Crude							
	Low	Reference		Reference		Reference	
	Middle	−0.084 (−0.197 to 0.029)	0.15	−0.134 (−0.247 to −0.022)	0.019	−0.195 (−0.308 to −0.082)	0.001
	High	−0.234 (−0.347 to −0.121)	<0.001	−0.271 (−0.383 to −0.158)	<0.001	−0.287 (−0.400 to −0.174)	<0.001
1							
	Low	Reference		Reference		Reference	
	Middle	−0.005 (−0.106 to 0.097)	0.93	0.002 (−0.099 to 0.102)	0.98	−0.076 (−0.181 to 0.029)	0.16
	High	−0.092 (−0.196 to 0.011)	0.08	−0.021 (−0.123 to 0.081)	0.69	−0.069 (−0.177 to 0.038)	0.21
2							
	Low	Reference		Reference		Reference	
	Middle	−0.016 (−0.118 to 0.086)	0.76	−0.009 (−0.110 to 0.092)	0.86	−0.082 (−0.188 to 0.024)	0.13
	High	−0.118 (−0.226 to −0.010)	0.033	−0.045 (−0.151 to 0.062)	0.41	−0.082 (−0.195 to 0.030)	0.15
3							
	Low	Reference		Reference		Reference	
	Middle	−0.004 (−0.098 to 0.096)	0.94	0.010 (−0.087 to 0.107)	0.84	−0.064 (−0.165 to 0.038)	0.22
	High	−0.117 (−0.210 to −0.011)	0.030	−0.040 (−0.143 to 0.062)	0.44	−0.085 (−0.192 to 0.023)	0.12
4							
	Low	Reference		Reference		Reference	
	Middle	0.002 (−0.099 to 0.102)	0.97	0.010 (−0.086 to 0.107)	0.83	−0.066 (−0.168 to 0.036)	0.20
	High	−0.105 (−0.212 to 0.002)	0.06	−0.036 (−0.139 to 0.067)	0.49	−0.084 (−0.193 to 0.025)	0.13
5							
	Low	Reference		Reference		Reference	
	Middle	0.000 (−0.094 to 0.098)	0.97	0.006 (−0.091 to 0.102)	0.91	−0.072 (−0.174 to 0.030)	0.16
	High	−0.106 (−0.213 to 0.001)	0.05	−0.039 (−0.142 to 0.064)	0.46	−0.087 (−0.195 to 0.022)	0.11

Regression coefficients (β) represent the SD difference in the cognitive domain scores as compared with participants with a low systolic BPV (lowest tertile of BPV). Model 1: age, sex, glucose metabolism status. Model 2: model 1+mean 24-h systolic blood pressure. Model 3: model 2+BMI, smoking behavior, alcohol use, educational level. Model 4: model 3+eGFR, total-to-high density lipoprotein cholesterol ratio, triglycerides, (individual classes of) antihypertensive medication, lipid-modifying medication. Model 5: model 4+prior cardiovascular disease, current depression. BMI indicates body mass index; BPV, blood pressure variability; eGFR, estimated glomerular filtration rate; and sBPV, systolic blood pressure variability.

−0.035]), and EF (−0.128; 95% CI, −0.235 to −0.021; Table 2; Figure 3). After adjustment for the covariates of model 5, the associations attenuated but remained statistically significant for IPS (−0.101; 95% CI, −0.200 to −0.002) and EF (−0.115; 95% CI, −0.220 to −0.011). In addition, MF was lower in individuals with high diastolic BPV as compared to those with low diastolic BPV but did not reach statistical significance (−0.094; 95% CI, −0.197 to 0.009).

Additional Analyses

Age, sex, and glucose metabolism did modify some associations between systolic or diastolic BPV and cognitive performance (Table S2). We did not detect a consistent interaction pattern over the domains of cognitive performance and, therefore, did not stratify the analyses.

After additional adjustment for moderate-to-vigorous physical activity, and waist circumference or waist-to-hip ratio instead of BMI, the associations between systolic or diastolic BPV and cognitive performance did not materially change (Tables S3–S9).

When we analyzed the individual systolic BPV-indices separately, within-visit and 24-hour systolic BPV and cognitive performance were not statistically significantly associated, whereas a high 7-day systolic BPV was statistically significantly associated with a lower performance in all cognitive domains as compared to the lowest tertile of 7-day systolic BPV. When we analyzed the individual diastolic BPV-indices separately, middle within-visit diastolic BPV was statistically significantly associated with lower EF as compared to the lowest tertile of within-visit diastolic BPV, high 24-hour diastolic BPV was statistically significantly associated with lower performance in all cognitive domains as compared to the lowest tertile of 24-hour diastolic BPV, and middle and high 7-day diastolic BPV was statistically significantly associated with

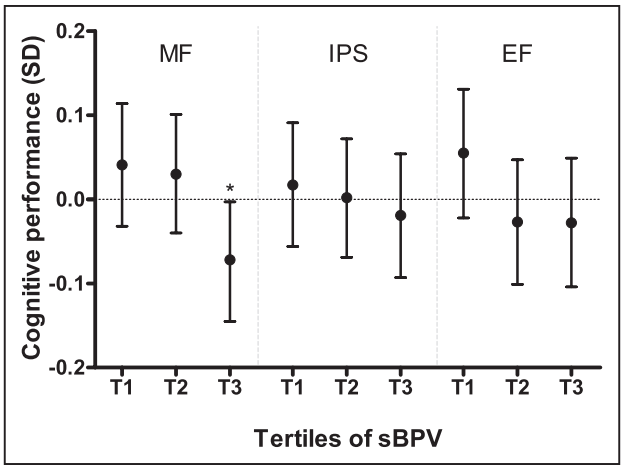

Figure 2. Estimated means of cognitive performance domains according to tertiles of systolic blood pressure variability (sBPV) after adjustment for the covariates of model 2. T1, T2, and T3 indicate tertiles with low, middle and high sBPV respectively. EF indicates executive functioning; IPS, information processing speed; and MF, memory function. Error bars represent 95% CI. *Statistically significant difference as compared to the lowest tertile (T1).

lower IPS and EF as compared to the lowest tertile of 7-day diastolic BPV (Tables S9–S14).

Discussion

Our study, performed in 40- to 75-year-old individuals, showed that greater very short–term to mid-term systolic and diastolic BPV differentially affects various domains of cognitive performance. First, greater diastolic BPV was associated with both lower IPS and EF and was marginally associated with lower MF. Second, greater systolic BPV was only marginally associated with a lower MF. All these associations were independent of mean systolic or diastolic BP, lifestyle factors, educational level, and cardiovascular risk factors. The observed effects are equivalent to ≈3 additional years of general aging. In terms of risk factors, in the light of previous studies performed in The Maastricht Study, the detrimental effects of greater systolic and diastolic BPV on cognitive performance are similar to the effects of the presence of microalbuminuria[31] and greater carotid arterial stiffness.[32]

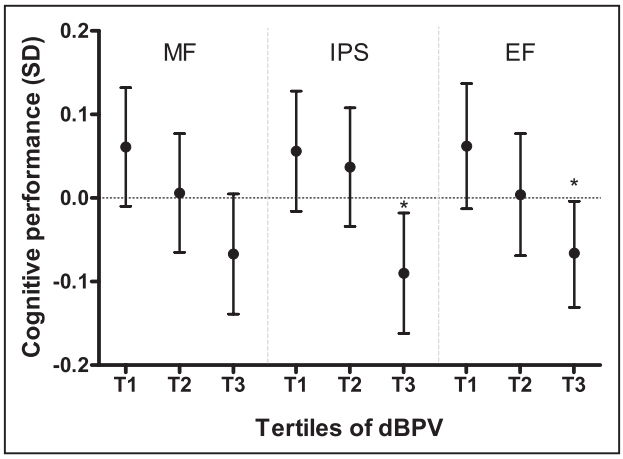

Figure 3. Estimated means of cognitive performance domains according to tertiles of diastolic blood pressure variability (dBPV) after adjustment for the covariates of model 2. T1, T2, and T3 indicate tertiles with low, middle and high dBPV respectively. EF indicates executive functioning; IPS, information processing speed; and MF, memory function. Error bars represent 95% CI. *Statistically significant difference as compared to the lowest tertile (T1).

Our findings are largely in line with previous studies, where greater systolic or diastolic BPV were associated with lower cognitive performance. However, previous studies have assessed only global cognitive performance, such as the Mini-Mental State Exam[15] or tested only one domain of cognitive performance.[19] Other studies have investigated specific study populations, such as individuals who already had dementia[10] or old to very old individuals.[11–14] In addition, many studies have investigated whether long-term BPV (ie, visit-to-visit) affects cognitive performance.[7–9,12,33] Our study thereby adds novelty to the literature, as our study was performed in community-dwelling individuals and applied an extensive cognitive test battery. In addition, we have shown that not only greater long-term BPV affects cognitive performance, but greater very short-term to mid-term diastolic BPV does so as well.

Interestingly, we observed a more pronounced effect of greater diastolic BPV on lower cognitive performance than systolic BPV. This may be explained by several mechanisms. First, diastolic BP is the main determinant of mean arterial pressure, and as such, excessive variation in diastolic BP may hamper perfusion and induce cerebral ischemia. Indeed, previous studies have shown that impaired cerebral blood flow may play a role in the progression of cerebral small vessel disease,[34] and impaired cerebral blood flow itself has been strongly associated with incident dementia.[35] Second, in a previous report, we observed that greater systolic BPV was associated with arterial stiffening, whereas diastolic BPV was not.[36] Indeed, it has been reported that arterial stiffening (carotid-to-femoral, brachial-to-ankle, and local carotid) was associated with cerebral small vessel disease, potentially via an increased pulsatile pressure load. However, associations between arterial stiffening and cognitive impairment were relatively weak, which suggests that additional factors other than cerebral small vessel disease alone may explain the mechanisms underlying cognitive impairment.[37]

We, therefore, speculate that greater systolic BPV may specifically cause more macrovascular damage (eg, aortic stiffening), whereas diastolic BPV is causing more microvascular damage (eg, cerebral small vessel disease).

We observed that greater systolic BPV was only marginally associated with MF, but not with IPS and EF, as opposed to diastolic BPV, which had an effect on all cognitive domains. We hypothesize that this might be because of the increased vulnerability to ischemia of watershed areas (eg, the parieto-temporal area), where perfusion is already poor.[38] Peaks in systolic BP may then induce autoregulatory vasoconstriction[6] and may lead to ischemia preferentially in the temporal areas, such as the hippocampus, which is an important brain region for memory consolidation.[39] Greater diastolic BPV, however, may reduce cerebral perfusion pressure in many brain regions and may, therefore, affect multiple cognitive functions.

The strengths of our study include the use of multiple BPV-indices and the well-characterized, large study population, which allowed us to adjust for a large series of confounders. In fact, model 5 may represent an overadjusted model, as depression, for instance, may lie in the causal pathway between

Table 3. Associations Between Diastolic Blood Pressure Variability and Various Domains of Cognitive Performance

Model	Composite dBPV	Cognitive Performance Domains					
		Memory Function		Information Processing Speed		Executive Function	
		β (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value
Crude							
	Low	Reference		Reference		Reference	
	Middle	−0.084 (−0.197 to 0.029)	0.15	−0.046 (−0.159 to 0.067)	0.42	−0.110 (−0.223 to 0.004)	0.06
	High	−0.219 (−0.332 to −0.106)	<0.001	−0.269 (−0.382 to −0.156)	<0.001	−0.226 (−0.379 to −0.153)	<0.001
1							
	Low	Reference		Reference		Reference	
	Middle	−0.040 (−0.140 to 0.060)	0.44	0.017 (−0.083 to 0.116)	0.74	−0.054 (−0.158 to 0.051)	0.31
	High	−0.111 (−0.212 to −0.009)	0.032	−0.108 (−0.209 to −0.008)	0.034	−0.121 (−0.227 to −0.016)	0.024
2							
	Low	Reference		Reference		Reference	
	Middle	−0.047 (−0.149 to 0.054)	0.36	−0.001 (−0.101 to 0.099)	0.98	−0.058 (−0.163 to 0.047)	0.28
	High	−0.123 (−0.226 to −0.019)	0.020	−0.137 (−0.239 to −0.035)	0.009	−0.128 (−0.235 to −0.021)	0.019
3							
	Low	Reference		Reference		Reference	
	Middle	−0.036 (−0.135 to 0.063)	0.48	0.019 (−0.077 to 0.114)	0.70	−0.040 (−0.141 to 0.060)	0.43
	High	−0.109 (−0.211 to −0.007)	0.036	−0.111 (−0.210 to −0.013)	0.026	−0.114 (−0.217 to −0.010)	0.031
4							
	Low	Reference		Reference		Reference	
	Middle	−0.037 (−0.137 to 0.062)	0.46	0.015 (−0.081 to 0.111)	0.76	−0.048 (−0.148 to 0.053)	0.35
	High	−0.095 (−0.198 to 0.008)	0.07	−0.101 (−0.200 to −0.002)	0.046	−0.113 (−0.217 to −0.009)	0.033
5							
	Low	Reference		Reference		Reference	
	Middle	−0.037 (−0.136 to 0.063)	0.47	0.016 (−0.079 to 0.112)	0.74	−0.048 (−0.149 to 0.052)	0.35
	High	−0.094 (−0.197 to 0.009)	0.07	−0.101 (−0.200 to −0.002)	0.046	−0.115 (−0.220 to −0.011)	0.030

Regression coefficients (β) represent the SD difference in the cognitive domain scores as compared with participants with a low diastolic BPV (lowest tertile of BPV). Model 1: age, sex, glucose metabolism status. Model 2: model 1+mean 24-h diastolic blood pressure. Model 3: model 2+BMI, smoking behavior, alcohol use, educational level. Model 4: model 3+eGFR, total-to-high density lipoprotein cholesterol ratio, triglycerides, (individual classes of) antihypertensive medication, lipid-modifying medication. Model 5: model 4+prior cardiovascular disease, current depression. BMI indicates body mass index; BPV, blood pressure variability; dBPV, diastolic blood pressure variability; and eGFR, estimated glomerular filtration rate.

greater BPV and lower cognitive performance. Nonetheless, the effects of BPV on cognitive performance changed minimally after model 3 and 4.

There were several limitations of this study. First, the cross-sectional nature of this study implies that any causal inference should be made with caution. The reverse association may hold true as well, as it can be hypothesized that lower cognitive performance could lead to worse medication adherence, which may then cause greater BPV.[40] Second, the design of this study required the population to be enriched with T2DM, and it might be argued that adjustment for glucose metabolism status may then not be sufficient. However, there was no consistent interaction pattern with glucose metabolism status, age, or sex. Third, participants with and without missing data differed. This may have led to an underestimation of our effect, as participants with missing data had a more adverse (cardiovascular) risk profile. Fourth, we cannot exclude the possibility of residual confounding, as, for example, family history of dementia[41,42] was not available. Fifth, the use of a composite BPV-index assumes that the individual BPV-indices share the same underlying pathophysiological mechanisms in lowering cognitive performance. Our results have shown that all individual BPV-indices were directionally similarly associated with cognitive performance, which implies that excessive BPV measured in any time frame, despite its different determinants, may damage the brain via similar mechanisms leading to lower cognitive performance. This justifies our approach with regard to the construction of a composite BPV-index.

Perspectives

Greater very short-term to mid-term diastolic and, to a lesser extent, systolic BPV may be a modifiable risk factor for cognitive deterioration in 40- to 75-year old, community-dwelling

individuals. The effects of greater BPV on cognitive performance were equivalent to 3 additional years of aging. In terms of risk factors, these effects were similar to the presence of microalbuminuria and carotid stiffness. Future research should focus on intervention trials dedicated to lowering BPV, and investigate whether it has a positive effect on preserving cognitive performance. If lowering BPV would indeed be beneficial, it could delay, or even prevent, cognitive decline in mid to later life.

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Disclosures

None.

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Novelty and Significance

What Is New?

- An important consequence of the globally increasing life expectancy will be that an increasing number of individuals will face age-related health problems, of which cognitive impairment is a major problem. To delay or prevent cognitive impairment, we investigated the association between very short- to mid-term blood pressure variability and cognitive performance.

What Is Relevant?

- Greater very short- to mid-term systolic and diastolic blood pressure variability (BPV) were differentially associated with lower cognitive performance, specifically:
  - Greater diastolic BPV was associated with both lower information processing speed and executive function and was marginally associated with lower memory function.
  - Greater systolic BPV was only marginally associated with a lower memory function.

Summary

Greater very short-term to mid-term diastolic, and to a lesser extent, systolic BPV are associated with lower cognitive performance. These effects were comparable to 3 additional years of aging. In short, these findings suggest that very short- to mid-term BPV may be a modifiable risk factor for cognitive impairment.